

Applicants: Jane H. Morse and James A. Knowles
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Amendments to the claims:

Certain claims have been amended and others canceled below without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims in a continuation application.

The following listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of claims:

1. (amended) A method of detecting whether a subject is predisposed to, or afflicted with, a pulmonary ~~disease~~ hypertension which comprises (1) obtaining a suitable sample containing bone morphogenetic protein receptor II or nucleic acid encoding same from the subject; and (2) detecting in the bone morphogenetic protein receptor II or nucleic acid encoding same ~~sample~~ whether a bone morphogenetic protein receptor-II mutation which is not present which is not present in wildtype bone morphogenetic protein receptor-II or nucleic acid encoding same,

wherein the presence of such a mutation indicates that the subject is predisposed, to or afflicted with, the pulmonary ~~disease~~ hypertension.

2. (amended) The method of claim 1, wherein the suitable sample ~~is~~ comprises ~~a nucleic acid sample, and the~~

~~mutation is detected in~~ a nucleic acid encoding bone morphogenetic protein receptor-II.

3. (amended) The method of claim 1, wherein the suitable sample ~~is one which~~ comprises a bone morphogenetic protein receptor-II polypeptide, ~~and the mutation is detected in the bone morphogenetic protein receptor-II polypeptide.~~

4. (amended) The method of claim 1, wherein the pulmonary disease hypertension is Primary Pulmonary Hypertension.

5. (original) The method of claim 4, wherein the Primary Pulmonary Hypertension is Familial Primary Pulmonary Hypertension.

6-50. (canceled)

51. (amended) A method of predicting an increased likelihood of a subject giving birth to twins or triplets which comprises:

- a) obtaining a suitable nucleic acid sample from the subject;
- b) detecting the presence of one copy of a ~~mutant~~ nucleic acid which encodes a mutant bone morphogenetic protein receptor-II polypeptide, thereby indicating that the subject is heterozygous

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for the ~~mutation~~ mutant bone morphogenetic protein
receptor II,

wherein heterozygosity predicts an increased likelihood
of the subject giving birth to twins or triplets.

52. (amended) A method of predicting an increased likelihood
of a pregnant subject having a miscarriage ~~prior to
giving birth to a child~~ which comprises:

- a) obtaining a suitable nucleic acid sample from the
subject;
- b) detecting the presence of two copies of a ~~mutant~~
nucleic acid, each of which encodes a mutant bone
morphogenetic protein receptor-II ~~polypeptide~~,
thereby indicating that the subject is homozygous
for the ~~mutation~~ mutant bone morphogenetic protein
receptor II,

wherein homozygosity predicts an increased likelihood of
the subject having a miscarriage ~~prior to giving birth
to a child~~.

53. (withdrawn)

54. (canceled)

55. (withdrawn)

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56. (amended) A method of detecting whether a subject is either predisposed to, or afflicted with, Familial Primary Pulmonary Hypertension which comprises:

- a) obtaining a suitable nucleic acid sample from the subject; and
- b) detecting the presence of a (GGC)₁₂ trinucleotide repeat at positions corresponding to positions -928 to -963 in the 5' end of the subject's bone morphogenetic protein receptor-II gene,

wherein the presence of the trinucleotide repeat indicates that the subject is either predisposed to, or afflicted with, Familial Primary Pulmonary Hypertension.

57. (withdrawn)

58. (canceled)

59-60. (withdrawn)

61-63. (canceled)

64. (new) The method of claim 2, wherein the mutation described relative to a difference from the sequence encoding wildtype bone morphogenetic protein receptor II set forth in SEQ ID NO:1 is selected from the group consisting of:

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- (1) a deletion of nucleotides having the sequence guanosine-guanosine-guanosine-guanosine-adenosine located at positions 1099-1103;
- (2) a deletion of a thymidine nucleotide located at position 2579;
- (3) a substitution of nucleotides having the sequence cytosine-thymidine-thymidine-thymidine located at positions 507-510 with nucleotides having the sequence adenosine-adenosine-adenosine;
- (4) a substitution of a cytosine nucleotide located at position 2617 with a thymidine nucleotide;
- (5) a substitution of nucleotides having the sequence adenosine-guanosine located at positions 690-691 with a thymidine nucleotide;
- (6) a substitution of a cytosine nucleotide located at position 1471 with a thymidine nucleotide;
- (7) a substitution of a guanosine nucleotide located at position 1472 with an adenosine nucleotide;
- (8) a deletion of nucleotides having the sequence adenosine-thymidine-thymidine-thymidine located at positions 1248-1251;
- (9) a substitution of a cytosine nucleotide located at position 994 with a thymidine;
- (10) a substitution of a thymidine nucleotide located at position 295 with a cytosine nucleotide;
- (11) a deletion of a guanosine nucleotide located at position 1097;

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- (12) a substitution of a guanosine nucleotide located at position 727 with a thymidine nucleotide;
- (13) a deletion of an adenosine nucleotide located at position 1214;
- (14) a deletion of nucleotides having the sequence adenosine-cytosine located at positions 2441-2442;
- (15) a substitution of a cytosine nucleotide located at position 2695 with a thymidine nucleotide;
- (16) a deletion of 21 nucleotides located at positions 189-209;
- (17) a substitution of a guanosine nucleotide located at position 296 with an adenosine nucleotide;
- (18) a substitution of a thymidine nucleotide located at position 250 with a cytosine nucleotide;
- (19) a substitution of a guanosine nucleotide located at position 1040 with an adenosine nucleotide.

65. (new) The method of claim 3, wherein the mutation described relative to a difference from the wildtype bone morphogenetic protein receptor II sequence set forth in SEQ ID NO:2 is selected from the group consisting of:

- (1) a mutation at a glutamic acid residue located at position 368 which causes the protein sequence thereon to be different from the wildtype bone morphogenetic protein receptor II sequence;
- (2) a mutation at an asparagine residue located at position 861 which causes the protein sequence thereon to

be different from the wildtype bone morphogenetic protein receptor II sequence;

(3) a substitution of a cysteine residue located at position 169 which causes premature termination of the protein sequence;

(4) a substitution of an arginine residue located at position 873 which causes premature termination of the protein sequence;

(5) a mutation at a lysine residue located at position 230 which causes the protein sequence thereon to be different from the wildtype bone morphogenetic protein receptor II sequence;

(6) a substitution of an arginine residue located at position 491 with a tryptophan residue;

(7) a substitution of an arginine residue located at position 491 with a glutamine residue;

(8) a substitution of a phenylalanine residue located at position 417 which causes premature termination of the protein sequence;

(9) a substitution of an arginine residue located at position 332 which causes premature termination of the protein sequence;

(10) a substitution of a cysteine residue located at position 99 with an arginine residue;

(11) a mutation at a proline residue located at position 366 which causes the protein sequence thereon to be different from the wildtype bone morphogenetic protein receptor II sequence;

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(12) a substitution of a glutamic acid residue located at position 243 which causes premature termination of the protein sequence;

(13) a mutation at an aspartic acid residue located at position 405 which causes the protein sequence thereon to be different from the wildtype bone morphogenetic protein receptor II sequence;

(14) a mutation at a histidine residue located at position 814 which causes the protein sequence thereon to be different from the wildtype bone morphogenetic protein receptor II sequence;

(15) a substitution of an arginine residue located at position 899 which causes premature termination of the protein sequence;

(16) a deletion of consecutive amino acids having the sequence serine-threonine-cysteine-tyrosine-glycine-leucine-tryptophan located at positions 64-70;

(17) a substitution of a cysteine residue located at position 99 with a tyrosine residue;

(18) a substitution of a cysteine residue located at position 84 with an arginine residue;

(19) a substitution of a cysteine residue located at position 347 with a tyrosine residue.